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(54) Title: INHIBITORS OF GLYCOGEN SYNTHASE KINASE 3

(57) Abstract: New pyrimidine or pyridine based compounds, compositions and methods of inhibiting the activity of glycogen synthase kinase (GSK3) *in vitro* and of treatment of GSK3 mediated disorders *in vivo* are provided. The methods, compounds and compositions of the invention may be employed alone, or in combination with other pharmacologically active agents in the treatment of disorders mediated by GSK3 activity, such as diabetes, Alzheimer's disease and other neurodegenerative disorders, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder, immunodeficiency or cancer.

INHIBITORS OF GLYCOGEN SYNTHASE KINASE 3

Field of the Invention

This invention relates to new pyrimidine and pyridine derivatives that inhibit the activity of glycogen synthase kinase 3 (GSK3) and to pharmaceutical compositions containing the compounds and to the use of the compounds and compositions, alone or in combination with other pharmaceutically active agents. The compounds and compositions provided by the present invention have utility in the treatment of disorders mediated by GSK3 activity, such as diabetes, Alzheimer's disease and other neurodegenerative disorders, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, especially cerebral ischemia, traumatic brain injury, bipolar disorder, immunodeficiency and cancer.

Background of the Invention

Glycogen synthase kinase 3 (GSK3) is a serine/threonine kinase for which two isoforms, α and β, have been identified. Woodgett, *Trends Biochem. Sci.*, **16**:177-81 (1991). Both GSK3 isoforms are constitutively active in resting cells. GSK3 was originally identified as a kinase that inhibits glycogen synthase by direct phosphorylation. Upon insulin activation, GSK3 is inactivated, thereby allowing the activation of glycogen synthase and possibly other insulin-dependent events, such glucose transport. Subsequently, it has been shown that GSK3 activity is also inactivated by other growth factors that, like insulin, signal through receptor tyrosine kinases (RTKs). Examples of such signaling molecules include IGF-1 and EGF. Saito et al., *Biochem. J.*, **303**:27-31 (1994); Welsh et al., *Biochem. J.* **294**:625-29 (1993); and Cross et al., *Biochem. J.*, **303**:21-26 (1994).

Agents that inhibit GSK3 activity are useful in the treatment of disorders that are mediated by GSK3 activity. In addition, inhibition of GSK3 mimics the activation of growth factor signaling pathways and consequently GSK3 inhibitors are useful in the treatment of diseases in which such pathways are insufficiently active. Examples of diseases that can be treated with GSK3 inhibitors are described below.

Diabetes.

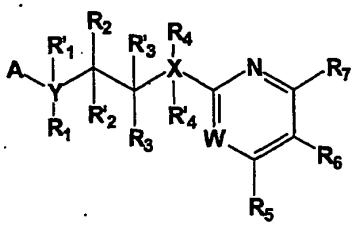
Diabetes mellitus is a serious metabolic disease that is defined by the presence of chronically elevated levels of blood glucose (hyperglycemia). This state of hyperglycemia is the result of a relative or absolute lack of activity of the peptide hormone, insulin. Insulin is produced and secreted by the ß cells of the pancreas. Insulin is reported to promote glucose utilization, protein synthesis, and the formation and storage of carbohydrate energy as glycogen. Glucose is stored in the body as glycogen, a form of polymerized glucose, which may be converted back into glucose to meet metabolism requirements. Under normal conditions, insulin is secreted at both a basal rate and at enhanced rates following glucose stimulation, all to maintain metabolic homeostasis by the conversion of glucose into glycogen.

The term diabetes mellitus encompasses several different hyperglycemic states. These states include Type 1 (insulin-dependent diabetes mellitus or IDDM) and Type 2 (non-insulin dependent diabetes mellitus or NIDDM) diabetes. The hyperglycemia present in individuals with Type 1 diabetes is associated with deficient, reduced, or nonexistent levels of insulin that are insufficient to maintain blood glucose levels within the physiological range. Conventionally, Type 1 diabetes is treated by administration of replacement doses of insulin, generally by a parental route. Since GSK3 inhibition stimulates insulin-dependent processes, it is consequently useful in the treatment of type 1 diabetes.

Type 2 diabetes is an increasingly prevalent disease of aging. It is initially characterized by decreased sensitivity to insulin and a compensatory elevation in circulating insulin concentrations, the latter of which is required to maintain normal blood glucose levels. Increased insulin levels are caused by increased secretion from the pancreatic beta cells, and the resulting hyperinsulinemia is associated with cardiovascular complications of diabetes. As insulin resistance worsens, the demand on the pancreatic beta cells steadily increases until the pancreas can no longer provide adequate levels of insulin, resulting in elevated levels of glucose in the blood. Ultimately, overt hyperglycemia and hyperlipidemia occur, leading to the devastating long-term complications associated with diabetes, including cardiovascular disease, renal failure and blindness. The exact mechanism(s) causing type 2 diabetes are unknown, but result in impaired glucose transport into skeletal muscle and increased hepatic glucose production,

That which is claimed is:

1. A compound having the structure:



(I)

wherein:

W is optionally substituted carbon or nitrogen;

X and Y are independently selected from the group consisting of nitrogen, oxygen, and optionally substituted carbon;

A is optionally substituted aryl or heteroaryl;

R_1, R'_1, R_2, R'_2, R_3, R'_3, R_4 and R'_4 are independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted loweralkyl, cycloloweralkyl, cyclicaminoalkyl, alkylaminoalkyl, loweralkoxy, amino, alkylamino, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, aryl and heteroaryl, and R'_1, R'_2, R'_3 and R'_4 are independently selected from the group consisting of hydrogen, and optionally substituted loweralkyl;

R_5 and R_7 are independently selected from the group consisting of hydrogen, halo, and optionally substituted loweralkyl, cycloalkyl, alkoxy, amino, aminoalkoxy, alkylamino, aralkylamino, heteroaralkylamino, arylamino, heteroarylamino cycloimido, heterocycloimido, amidino, cycloamidino, heterocycloamidino, guanidinyl, aryl, biaryl, heteroaryl, heterobiaryl, heterocycloalkyl, and arylsulfonamido;

R_6 is selected from the group consisting of hydrogen, hydroxy, halo, carboxyl, nitro, amino, amido, amidino, imido, cyano, and substituted or unsubstituted loweralkyl, loweralkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteraralkylcarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkylaminocarbonyloxy, arylaminocarbonyloxy, formyl, loweralkylcarbonyl, loweralkoxycarbonyl, aminocarbonyl, aminoaryl, alkylsulfonyl, sulfonamido, aminoalkoxy, alkylamino, heteroarylamino, alkylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino cycloamido,

cyclothioamido, cycloamidino, heterocycloamidino, cycloimido, heterocycloimido, guanidinyl, aryl, heteroaryl, heterocyclo, heterocycloalkyl, arylsulfonyl and arylsulfonamido;

and the pharmaceutically acceptable salts thereof.

2. A compound of claim 1 wherein at least one of X and Y is nitrogen.

3. A compound of claim 2 wherein one of X and Y is nitrogen and the other of X and Y is optionally substituted carbon.

4. A compound of claim 2 wherein one of X and Y is nitrogen and the other of X and Y is oxygen.

5. A compound of claim 2, wherein both X and Y are nitrogen.

6. A compound of claim 1, wherein A is an aromatic ring having from 3 to 10 carbon ring atoms and optionally 1 or more ring heteroatoms.

7. A compound of claim 6, wherein A is optionally substituted carbocyclic aryl.

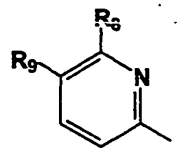
8. A compound of claim 6, wherein A is optionally substituted heteroaryl.

9. A compound of claim 6, wherein A is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl.

10. A compound of claim 6, wherein A is substituted with at least one and not more than 3 substitution groups.

11. A compound of claim 10, wherein said substitution groups are independently selected from the group consisting of nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, halologweralkyl, loweralkoxy, halologweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aminoalkyl and cyanoalkyl.

12. A compound of claim 6 wherein A has the formula:



(II)

wherein R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidinyl, sulfonamido, carboxyl, formyl, loweralkyl, aminoloweralkyl, loweralkylaminoloweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl,loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aryl and, aralkyl.

13. A compound of claim 9, wherein A is selected from the group consisting of aminopyridyl, nitropyridyl, aminonitropyridyl, cyanopyridyl, cyanothiazolyl, aminocyanopyridyl, trifluoromethylpyridyl, methoxypyridyl, methoxynitropyridyl, methoxycyanopyridyl and nitrothiazolyl.

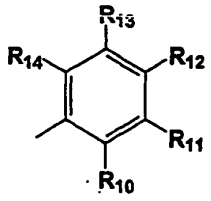
14. A compound of claim 1, wherein at least one of R_1, R'_1, R_2, R'_2, R_3, R_3', R_4, and R'_4 is substituted loweralkyl selected from the group consisting of hydrogen, unsubstituted or substituted loweralkyl, haloloweralkyl, heterocycloaminoalkyl, and loweralkylaminoloweralkyl.

15. A compound of claim14, wherein at least one of R_1, R'_1, R_2, R'_2, R_3, R_3', R_4, and R'_4 is loweralkylaminoloweralkyl.

16. A compound of claim14, wherein R_1, R'_1, R_2, R'_2, R_3, R_3'and R_4 are hydrogen and R'_4 is selected from the group consisting of hydrogen, methyl, ethyl, aminoethyl, dimethylaminoethyl, pyridylethyl, piperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylethyl.

17. A compound of claim 1, wherein at least one of R_5 and R_7 is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl and biaryl.

18. A compound of claim 17 wherein at least one of R_5 and R_7 is a substituted or unsubstituted moiety of the formula:



(III)

wherein R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, carboxyl, hydroxy, and optionally substituted loweralkyl, loweralkoxy, loweralkoxyalkyl, halologweralkyl, halologweralkoxy, aminoalkyl, alkylamino, aminoalkylalkynyl, alkylaminoalkylalkynyl, alkylthio, alkylcarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino aminocarbonyl, loweralkylaminocarbonyl, aminoaralkyl, , loweralkylaminoalkyl, aryl, heteroaryl, cycloheteroalkyl, aralkyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxyalkyl, alkylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, aralkycarbonyloxyalkyl, and heteroaralkcarbonyloxyalkyl.

19. A compound of claim 18 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, halologweralkyl, aminocarbonyl, alkylaminocarbonyl and cyano.

20. A compound of claim 18 wherein R_{11}, R_{13}, and R_{14} are hydrogen and R_{10} and R_{12} are independently selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, halologweralkyl and cyano.

21. A compound of claim 18 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is heteroaryl.

22. A compound of claim 18 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is a heterocycloalkyl.

23. A compound of claim 18 wherein at least one of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are halo and the remainder of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are hydrogen.

24. A compound of claim 18 wherein at least one of R_5 and R_7 is selected from the group consisting of dichlorophenyl, difluorophenyl, trifluoromethylphenyl, chlorofluorophenyl, bromochlorophenyl, ethylphenyl, methylchlorophenyl, imidazolylphenyl, cyanophenyl, morphlinophenyl and cyanochlorophenyl.

25. A compound of claim 1, wherein R_6 is substituted alkyl selected from the group consisting of aralkyl, hydroxyalkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonyl-aminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

26. A compound of claim 1, wherein R_6 is substituted amino selected from the group consisting of alkylamino, alkylcarbonylamino, alkoxycarbonylamino, arylalkylamino, arylcarbonylamino, alkylthiocarbonylamino, arylsulfonylamino, heteroarylamino alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylcarbonylamino, and heteroaralkylcarbonylamino.

27. A compound of claim 1, wherein R_6 is selected from the group consisting of unsubstituted or substituted aminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and alkylaminoalkyloxycarbonyl.

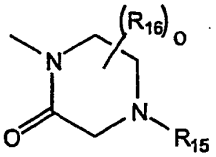
28. A compound of claim 1, wherein R_6 is selected from the group consisting of amidino, guanidino, cycloimido, heterocycloimido, cycloamido, heterocycloamido, cyclothioamido and heterocyclooloweralkyl.

29. A compound of claim 1, wherein R_6 is aryl.

30. A compound of claim 1, wherein R_6 is heteroaryl.

31. A compound of claim 30, wherein R_6 is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, piperazinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, pyrrolylpyridyl, benzothiazolyl, benzopyridyl, benzotriazolyl, and benzimidazolyl.

32. A compound of claim 31, wherein R_6 is a monoketopiperazinyl group having the structure:



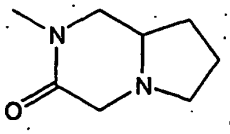
wherein R_{15} and R_{16} are independently selected from the group consisting of hydrogen, loweralkyl, loweralkynyl, aryl, heteroaryl, aryllowerakyl, loweralkylaryllowerakyl, halolowerakyl, haloaryllowerakyl carbocyclic and

heterocyclic; or R_{16} can be taken with another R_{16} or with R_{15} to form a carbocyclic, heterocyclic or aryl ring; and o is an integer between 1 and 6.

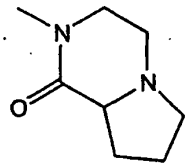
33. A compound of claim 32, wherein R_{15} is loweralkyl.

34. A compound of claim 33, wherein R_{15} is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl and t-butyl.

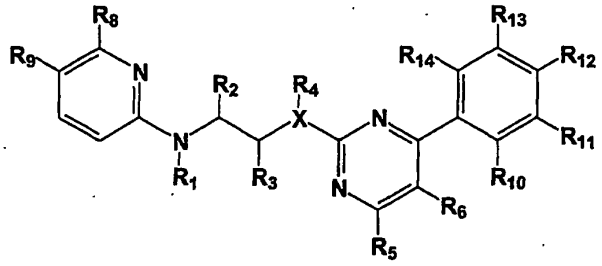
35. A compound of claim 32, wherein R_{15} is taken with R_{16} to form a group having the structure:



36. A compound of claim 32, wherein R_{15} is taken with R_{16} to form a group having the structure:



37. A compound having the structure:



(IV)

wherein:

X is selected from the group consisting of nitrogen, oxygen, and optionally substituted carbon;

R_1, R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted loweralkyl, cycloloweralkyl, cyclicaminoalkyl, alkylaminoalkyl, loweralkoxy, amino, alkylamino, alkylcarbonyl,

arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, aryl and heteroaryl;

R_5 is selected from the group consisting of hydrogen, halo, and optionally substituted loweralkyl, cycloalkyl, alkoxy, amino, aminoalkoxy, alkylamino, aralkylamino, heteroaralkylamino, arylamino, heteroarylamino cycloimido, heterocycloimido, amidino, cycloamidino, heterocycloamidino, guanidinyl, aryl, biaryl, heteroaryl, heterobiaryl, heterocycloalkyl, and arylsulfonamido;

R_6 is selected from the group consisting of hydrogen, hydroxy, halo, carboxyl, nitro, amino, amido, amidino, imido, cyano, and substituted or unsubstituted loweralkyl, loweralkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteraralkylcarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkylaminocarbonyloxy, arylaminocarbonyloxy, formyl, loweralkylcarbonyl, loweralkoxycarbonyl, aminocarbonyl, aminoaryl, alkylsulfonyl, sulfonamido, aminoalkoxy, alkylamino, heteroarylamino, alkylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino cycloamido, cyclothioamido, cycloamidino, heterocycloamidino, cycloimido, heterocycloimido, guanidinyl, aryl, heteroaryl, heterocyclo, heterocycloalkyl, arylsulfonyl and arylsulfonamido;

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidinyl, sulfonamido, carboxyl, formyl, loweralkyl, aminoloweralkyl, loweralkylaminoloweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aryl and, aralkyl; and

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, carboxyl, hydroxy, and optionally substituted loweralkyl, loweralkoxy, loweralkoxyalkyl, haloloweralkyl, haloloweralkoxy, aminoalkyl, alkylamino, alkylthio, alkylcarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino aminocarbonyl, loweralkylaminocarbonyl, aminoaralkyl, loweralkylaminoalkyl, aryl, heteroaryl, cycloheteroalkyl, aralkyl, and alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxyalkyl, alkyloxycarbonylalkyl, heteroarylcarbonyloxyalkyl, aralkycarbonyloxyalkyl, heteroaralkylcarbonyloxyalkyl;

and the pharmaceutically acceptable salts thereof.

38. A compound of claim 37 wherein X is nitrogen.

39. A compound of claim 37 wherein X is oxygen.

40. A compound of claim 37, wherein at least one of R_8 and R_9 is selected from the group consisting of nitro, amino, cyano, trifluoromethyl and loweralkoxy.

41. A compound of claim 37, wherein at least one of R_1, R_2, R_3 and R_4 is substituted loweralkyl selected from the group consisting of hydrogen, unsubstituted loweralkyl, halologweralkyl, heterocycloaminoalkyl, aminoloweralkyl and loweralkylaminoloweralkyl.

42. A compound of claim 37, wherein at least one of R_1, R_2, R_3 and R_4 is loweralkylaminoloweralkyl.

43. A compound of claim 37, wherein R_1, R_2, and R_3 are hydrogen and R_4 is selected from the group consisting of hydrogen, methyl, ethyl, aminoethyl, dimethylaminoethyl, pyridylethyl, piperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylethyl.

44. A compound of claim 37, wherein R_5 is selected from the group consisting of hydrogen and substituted and unsubstituted aryl, heteroaryl and biaryl.

45. A compound of claim 37 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, halologweralkyl, aminocarbonyl, alkylaminocarbonyl and cyano.

46. A compound of claim 37 wherein R_{11}, R_{13}, and R_{14} are hydrogen and R_{10} and R_{12} are independently selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, halologweralkyl, aminocarbonyl and cyano.

47. A compound of claim 37 wherein R_{10} is hydrogen or halo, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is heteroaryl.

48. A compound of claim 37 wherein R_{10} is hydrogen or halo, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is a heterocycloalkyl.

49. A compound of claim 37 wherein at least one of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are halo and the remainder of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are hydrogen.

50. A compound of claim 37 wherein R_{10}, R_{11}, R_{12}, R_{13}, and R_{14}, taken together with the phenyl ring of structure IV, form a moiety selected from the group consisting of dichlorophenyl, difluorophenyl, trifluoromethylphenyl, chlorofluorophenyl, bromochlorophenyl, ethylphenyl, methylchlorophenyl, imidazolylphenyl, cyanophenyl, morpholinophenyl and cyanochlorophenyl.

51. A compound of claim 37, wherein R_6 is substituted alkyl selected from the group consisting of aralkyl, hydroxyalkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonylaminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

52. A compound of claim 37, wherein R_6 is substituted amino selected from the group consisting of alkylamino, alkylcarbonylamino, alkoxycarbonylamino, arylalkylamino, arylcarbonylamino, alkylthiocarbonylamino, arylsulfonylamino, heteroarylamino alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylcarbonylamino, and heteroaralkylcarbonylamino.

53. A compound of claim 37, wherein R_6 is substituted carbonyl selected from the group consisting of unsubstituted or substitutedaminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and alkylaminoalkyloxycarbonyl.

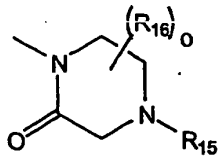
54. A compound of claim 37, wherein R_6 is selected from the group consisting of amidino, guanidino, cycloimido, heterocycloimido, cycloamido, heterocycloamido, cyclothioamido and heterocyclololoweralkyl.

55. A compound of claim 37, wherein R_6 is aryl.

56. A compound of claim 37, wherein R_6 is heteroaryl.

57. A compound of claim 56, wherein R_6 is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, pyrrolindinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, pyrrolylpyridyl, benzothiazolyl, benzopyridyl, benzotriazolyl, and benzimidazolyl.

58. A compound of claim 57, wherein R_6 is a monoketopiperazinyl group having the structure:

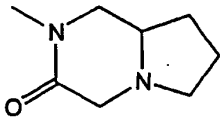


wherein R_{15} and R_{16} are independently selected from the group consisting of hydrogen, loweralkyl, loweralkynyl, aryl, heteroaryl, aryllowerakyl, loweralkylaryllowerakyl, halololoweralkyl, haloaryllowerakyl carbocyclic and heterocyclic; or R_{16} can be taken with another R_{16} or with R_{15} to form a carbocyclic, heterocyclic or aryl ring; and o is an integer between 1 and 6.

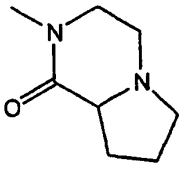
59. A compound of claim 58, wherein R_{15} is loweralkyl.

60. A compound of claim 59, wherein R_{15} is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl and t-butyl.

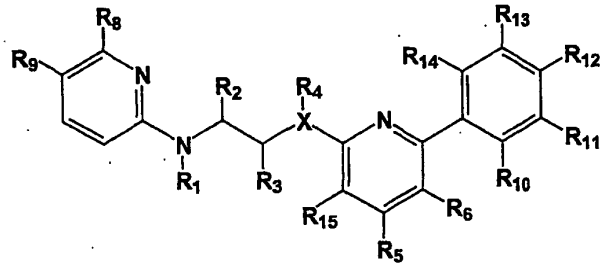
61. A compound of claim 58, wherein R_{15} is taken with R_{16} to form a group having the structure:



62. A compound of claim 58, wherein R_{15} is taken with R_{16} to form a group having the structure:



63. A compound having the structure:



(V)

wherein:

X is selected from the group consisting of nitrogen, oxygen, and optionally substituted carbon;

R_1, R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted loweralkyl, cyclooweralkyl, cyclicaminoalkyl, alkylaminoalkyl, loweralkoxy, amino, alkylamino, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, aryl and heteroaryl;

R_5 is selected from the group consisting of hydrogen, halo, and optionally substituted loweralkyl, cycloalkyl, alkoxy, amino, aminoalkoxy, alkylamino, aralkylamino, heteroaralkylamino, arylamino, heteroarylamino cycloimido, heterocycloimido, amidino, cycloamidino, heterocycloamidino, guanidinyl, aryl, biaryl, heteroaryl, heterobiaryl, heterocycloalkyl, and arylsulfonamido;

R_6 is selected from the group consisting of hydrogen, hydroxy, halo, carboxyl, nitro, amino, amido, amidino, imido, cyano, and substituted or unsubstituted loweralkyl, loweralkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteraralkylcarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkylaminocarbonyloxy, arylaminocarbonyloxy, formyl, loweralkylcarbonyl, loweralkoxycarbonyl, aminocarbonyl, aminoaryl, alkylsulfonyl, sulfonamido, aminoalkoxy, alkylamino, heteroarylamino, alkylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino cycloamido, cyclothioamido, cycloamidino, heterocycloamidino, cycloimido, heterocycloimido, guanidinyl, aryl, heteroaryl, heterocyclo, heterocycloalkyl, arylsulfonyl and arylsulfonamido;

R_8 and R_9 are independently selected from the group consisting of hydrogen, hydroxy, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidinyl, sulfonamido, carboxyl, formyl, loweralkyl, aminoloweralkyl, loweralkylaminoloweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aryl and, aralkyl; and

R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, carboxyl, hydroxy, and optionally substituted loweralkyl, loweralkoxy, loweralkoxyalkyl, haloloweralkyl, haloloweralkoxy, aminoalkyl, alkylamino, alkylthio, alkylamino, aralkylamino, heteroaralkylamino, arylamino, heteroarylamino aminocarbonyl, loweralkylaminocarbonyl, aminoaralkyl, loweralkylaminoalkyl, aryl, heteroaryl, cycloheteroalkyl, aralkyl, and alkylcarbonyloxy,

arylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxyalkyl, alkylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, aralkycarbonyloxyalkyl, heteroaralkylcarbonyloxyalkyl;

R_{15} is selected from the group consisting of hydrogen, nitro, cyano, amino, alkyl, halo, haloloweralkyl, alkyloxycarbonyl, aminocarbonyl, alkylsulfonyl and arylsulfonyl;

and the pharmaceutically acceptable salts thereof.

64. A compound of claim 63 wherein X is nitrogen.

65. A compound of claim 63 wherein X is oxygen.

66. A compound of claim 63, wherein at least one of R_8 and R_9 is selected from the group consisting of nitro, amino, cyano, trifluoromethyl and loweralkoxy.

67. A compound of claim 63, wherein at least one of R_1, R_2, R_3 and R_4 is substituted loweralkyl selected from the group consisting of hydrogen, unsubstituted loweralkyl, haloloweralkyl, heterocycloaminoalkyl, and loweralkylaminoloweralkyl.

68. A compound of claim 63, wherein at least one of R_1, R_2, R_3 and R_4 is loweralkylaminoloweralkyl.

69. A compound of claim 63, wherein R_1, R_2, and R_3 are hydrogen and R_4 is selected from the group consisting of hydrogen, methyl, ethyl, aminoethyl, dimethylaminoethyl, pyridylethyl, piperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylethyl.

70. A compound of claim 63 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, halooloweralkyl, aminocarbonyl, alkylaminocarbonyl and cyano.

71. A compound of claim 63 wherein R_{11}, R_{13}, and R_{14} are hydrogen and R_{10} and R_{12} are independently selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, halooloweralkyl, aminocarbonyl and cyano.

72. A compound of claim 63 wherein R_{10} is hydrogen or halo, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is heteroaryl.

73. A compound of claim 63 wherein R_{10} is hydrogen or halo, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is a heterocycloalkyl.

74. A compound of claim 63 wherein at least one of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are halo and the remainder of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are hydrogen.

75. A compound of claim 63 wherein R_{10}, R_{11}, R_{12}, R_{13}, and R_{14}, taken together with the phenyl ring of structure IV, form a moiety selected from the group consisting of dichlorophenyl, difluorophenyl, trifluoromethylphenyl, chlorofluorophenyl, bromochlorophenyl, ethylphenyl, methylchlorophenyl, imidazolylphenyl, cyanophenyl, morpholinophenyl and cyanochlorophenyl.

76. A compound of claim 63, wherein R_6 is substituted alkyl selected from the group consisting of aralkyl, hydroxyalkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonylaminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

77. A compound of claim 63, wherein R_6 is substituted amino selected from the group consisting of alkylamino, alkylcarbonylamino, alkoxycarbonylamino, arylalkylamino, arylcarbonylamino, alkylthiocarbonylamino, arylsulfonylamino, heteroarylamino alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylcarbonylamino, and heteroaralkylcarbonylamino.

78. A compound of claim 63, wherein R_6 is selected from the group consisting of unsubstituted or substitutedaminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and alkylaminoalkyloxycarbonyl.

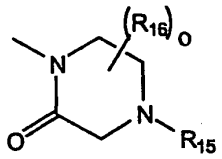
79. A compound of claim 63, wherein R_6 is selected from the group consisting of amidino, guanidino, cycloimido, heterocycloimido, cycloamido, heterocycloamido, cyclothioamido and heterocyclololoweralkyl.

80. A compound of claim 63, wherein R_6 is aryl.

81. A compound of claim 63, wherein R_6 is heteroaryl.

82. A compound of claim 81, wherein R_6 is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, pyrrolindinyl, piperazinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, pyrrolylpyridyl, benzothiazolyl, benzopyridyl, benzotriazolyl, and benzimidazolyl.

83. A compound of claim 82, wherein R_6 is a monoketopiperazinyl group having the structure:

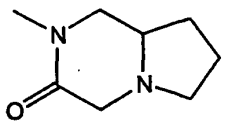


wherein R_{15} and R_{16} are independently selected from the group consisting of hydrogen, loweralkyl, loweralkynyl, aryl, heteroaryl, aryllowerallkyl, loweralkylaryllowerallkyl, halolowerallkyl, haloaryllowerallkyl carbocyclic and heterocyclic; or R_8 can be taken with another R_{16} or with R_{15} to form a carbocyclic, heterocyclic or aryl ring; and o is an integer between 1 and 6.

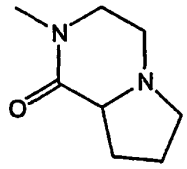
84. A compound of claim 83, wherein R_{15} is loweralkyl.

85. A compound of claim 84, wherein R_{15} is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl and t-butyl.

86. A compound of claim 83, wherein R_{15} is taken with R_{16} to form a group having the structure:



87. A compound of claim 83, wherein R_{15} is taken with R_{16} to form a group having the structure:



88. A composition comprising an amount of a compound of claim 1 effective to modulate GSK3 activity in a human or animal subject when administered thereto, together with a pharmaceutically acceptable carrier.

89. A composition comprising an amount of a compound of claim 37 effective to modulate GSK3 activity in a human or animal subject when administered thereto, together with a pharmaceutically acceptable carrier.

90. A composition comprising an amount of a compound of claim 63 effective to modulate GSK3 activity in a human or animal subject when administered thereto, together with a pharmaceutically acceptable carrier.

91. A method of inhibiting GSK3 activity in a human or animal subject, comprising administering to the human or animal subject a composition of claim 88.

92. A method of inhibiting GSK3 activity in a human or animal subject, comprising administering to the human or animal subject a composition of claim 89.

93. A method of inhibiting GSK3 activity in a human or animal subject, comprising administering to the human or animal subject a composition of claim 90.

94. A method of treating a cell comprising administering to the cell an amount of a compound of claim 1 effective to inhibit GSK3 activity in the cell.

95. A method of treating a cell comprising administering to the cell an amount of a compound of claim 37 effective to inhibit GSK3 activity in the cell.

96. A method of treating a cell comprising administering to the cell an amount of a compound of claim 63 effective to inhibit GSK3 activity in the cell.

97. A method for treating a GSK3-mediated disorder in a human or animal subject, comprising administering to the human or animal subject an amount of a composition of claim 88 effective to inhibit GSK3 activity in the subject.

98. A method of claim 97, wherein the composition is administered by a mode of administration selected from the group consisting of oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intrathecal, buccal, sublingual, intranasal, and rectal administration.

99. A method of claim 97, wherein said GSK3-mediated disorder is selected from the group consisting of diabetes, Alzheimer's disease, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder, immunodeficiency and cancer.

100. A method of claim 99, which further comprises administering to the subject one or more additional active agents.

101. A method of claim 100, wherein the GSK3-mediated disorder is diabetes and the additional active agent is selected from the group consisting of insulin, troglitazone, rosiglitazone, pioglitazone, glipizide and metformin.

102. A compound of claim 1, 37 or 58 for use as a pharmaceutical.

103. Use of a compound of claim 1, 37 or 63 in the manufacture of a medicament for the treatment of diabetes, Alzheimer's disease and other neurodegenerative disorders, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder or cancer.